Safety and efficacy of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in pediatric patients with hemophilia B: A review of results from phase 3 trial studies

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Introduction

- Hemophilia B is a recessive X-linked congenital bleeding disorder resulting from a deficiency of coagulation factor IX (FIX), causing either spontaneous or trauma-related bleeds and hemarthrosis from impaired hemostasis[1]
- Recombinant fusion protein linking coagulation with albumin (rIX-FP) has been shown to be effective and well tolerated in both adults and children with hemophilia B, even with prolonged dosing intervals[2–4]
- Clinical trials have previously combined adolescent data with the adult population, per protocol[3]
- There is no literature yet published that reports the efficacy and safety for defined pediatric populations, including adolescents up to 18 years old

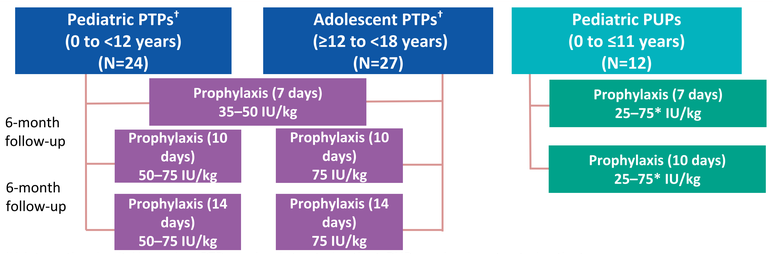
Objective

- **This post hoc analysis aims to demonstrate the safety and efficacy of rIX-FP for routine clinical use in pediatric and adolescent patients, including previously untreated patients (PUPs)**

Methods

- Data from previously treated patients (PTPs) and PUPs with severe hemophilia B (FIX ≤2%) aged ≤18 years, who participated in the PROLONG-9FP clinical trial program (NCT01101496274, NCT01662531, and NCT02053792) were included in this post hoc analysis
- PTPs received weekly rIX-FP prophylaxis (35–50 IU/kg)
  - If patients were well controlled, they could extend to a 10-day then a 14-day regimen (50–75 IU/kg) at any 6-month follow-up
- PUPs received a weekly rIX-FP prophylaxis regimen (25–50 IU/kg) for ≥50 exposure days, but dosing intervals, if appropriate, could be individualized
- Bleeding rates (frequency, type, severity, and location), adverse events (AEs; frequency, type, severity, and relationship to treatment), inhibitor development and pharmacokinetic (PK) assessments were performed approximately every six weeks at participating treatment centers
- The study design is presented in **Figure 1**

Figure 1. Study design and dosing regimen



IU, international unit; N, number; PTP, previously treated patient, PUP, previously untreated patient.

†Patients with well-controlled symptoms could extend their dosing interval at any 6-month follow-up

*An rIX-FP dose > 50 IU/kg (up to a maximum dose of 75 IU/kg) was acceptable if the FIX activity trough level was< 5% at Day 7 and a higher trough level was necessary to prevent spontaneous bleeding

Results

- This analysis included 24 pediatric PTPs (0 to <12 years), 7 adolescent PTPs (≥12 to <18 years) and 12 pediatric PUPs (0 to ≤11 years)

Bleeding rate outcomes

- Bleeding rates across all regimens and cohorts are presented in **Table 1**
- The mean (standard deviation [SD]) annualized bleeding rate (ABR), annualized spontaneous bleeding rate (AsBR) and annualized joint bleeding rate (AjBR) were comparable for both pediatric (<12 years) and for adolescent (≥12 to <18 years) PTPs when switching from a 7-day to a 10-, or a 14-day regimen
- In the pediatric PUP cohort, the mean ABR was improved for the 10-day regimen compared to the 7-day regimen

Table 1. Overview of bleeding rate data for 7-, 10-, and 14-day regimens on rIX-FP prophylaxis

	Pediatric PTPs (0 to <12 years) (N=24*†)			Adolescent PTPs (≥12 to <18 years) (N=7†)			Pediatric PUPs (0 to ≤11 years) (N=12**)	
Regimen	7-day (n=21)	10-day (n=8)	14-day (n=8)	7-day (n=7)	10-day (n=3)	14-day (n=3)	7-day (n=9)	10-day (n=1)
Mean ABR (SD)	3.3 (3.6)	4.0 (3.6)	4.7 (3.1)	0.7 (1.2)	1.6 (1.5)	1.3 (2.3)	1.2 (1.1)	1.0 (NC)
Mean AsBR (SD)	0.6 (1.3)	1.6 (2.5)	1.7 (2.0)	0.3 (0.7)	0.0 (0.0)	0.3 (0.6)	N/A	N/A
Mean AjBR (SD)	1.8 (2.9)	2.5 (2.8)	2.0 (1.7)	0.3 (0.9)	0.5 (0.9)	1.3 (2.3)	N/A	N/A

ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate; N/n, number; N/A, not applicable; NC, not calculable; PTP, previously treated patient; PUP, previously untreated patient; rIX-FP, recombinant factor IX fusion protein; SD, standard deviation.

*Efficacy data per regimen from the Phase 3b extension study NCT02053792.

†Pediatric and adolescent PTP datasets include patients that were on prophylaxis treatment for ≥12 weeks; the same patient could contribute data to multiple regimens based on the duration of treatment received.

**Pediatric PUP dataset includes only patients that were on prophylaxis treatment for >6 months (>183 days).

Safety outcomes

- Overall, 319 AEs were reported, of which 3 were considered treatment-emergent AEs (TEAEs) related to rIX-FP **(Table 2)**
- One 11-year-old PUP (8.3%) was discontinued from the study after 39 EDs following two mild hypersensitivity reactions related to rIX-FP; at the time of discontinuation the patient had a peak inhibitor titer of 66.0 BU/mL
  - The patient was switched from a 7-day prophylaxis regimen to an intensified treatment with rIX-FP following inhibitor development
  - Genetic mutation data showed that he had a large deletion involving exons 7 and 8 of the *F9* gene
- The other TEAEs related to rIX-FP included one injection site hematoma and one mild rash, both resolved

Table 2. Adverse events reported for patients who received at least one dose of rIX-FP

	Pediatric PTPs (0 to <12 years) (N=27)	Adolescent PTPs (≥12 to <18 years) (N=7)	Pediatric PUPs (0 to ≤11 years) (N=12)
Events, N	152	58	109
Intensity, N (%):			
Mild	126 (83)	52 (90)	86 (79)
Moderate	23 (15)	3 (5)	21 (19)
Severe	3 (2)	3 (5)	2 (2)
TEAE related to rIX-FP, N (%)	0	1 (2)†	2 (2)*

†TEAE reported was an injection site hematoma which resolved

*The TEAEs reported included hypersensitivity in the 11-year-old PUP who later developed a high titer inhibitor during intensified treatment and discontinued from the study, the other was recorded as a mild rash which resolved

AEs, adverse events; N, number; PTP, previously treated patient; PUPs, previously treated patients; rIX-FP, recombinant factor IX fusion protein; TEAE, treatment-emergent adverse event.

PK outcomes

- The mean incremental recovery (IR) rates following a single 50 IU/kg rIX-FP dose were >1.0 across all cohorts **(Table 3)**
- Mean (% coefficient of variance [CV]) terminal half-life values reported for the pediatric < 12 years and adolescent PTP cohorts were 91.4 (17.5) and 70.5 (33.8), respectively **(Table 3)**
- The mean steady-state trough FIX levels reported on a 7-day prophylaxis regimen were >10 IU/dL across all cohorts **(Table 3)**

Table 3. Pharmacokinetic parameters and Factor IX activity

Parameter	Pediatric PTPs (0 to <12 years) N=27*	Adolescent PTPs (≥12 to <18 years) N=6	Pediatric PUPs (0 to ≤11 years) N=8
Baseline-corrected PK parameters†, mean (%CV)			
IR (IU/dL)/(IU/kg)	1.0 (22.5)	1.1 (27.7)	1.2 (30.3)
Terminal half-life (h)	91.4 (17.5)	70.5 (33.8)	N/A
Steady-state trough FIX activity on 7-day prophylaxis regimen			
Steady-state trough FIX activity, mean (SD) IU/dL	15.1 (4.1)	18.1 (7.7)	12.49 (6.1**)

%CV, percent coefficient of variation; FIX, factor IX; h, hours; IR, incremental recovery; IU, international unit; N, number; N/A, not applicable; PK, pharmacokinetic; PTP, previously treated patient; PUP, previously untreated patient; rIX-FP, recombinant factor IX fusion protein; SD, standard deviation.

†PK parameters were measured after a single 50 IU/kg rIX-FP dose

*IR and terminal half-life data from the Phase 3 extension study NCT01662531, and trough data from the Phase 3b extension study NCT02053792

**Steady-state trough FIX activity data were only available for 7/12 patients.

Conclusions

- **rIX-FP is an effective treatment option, maintaining trough levels >10 IU/dL with 7-day dosing, in addition to a favorable safety profile for patients with hemophilia B aged 0 to 18 years, including PUPs**

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Conflicts of interest

DD and **WS:** are employees of CSL Behring; **HC:** Research support from Biomarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Shire/Takeda, SOBI; honoraria from Biomarin, CSL Behring, Novo Nordisk, Pfizer, Roche, SOBI; travel support from Biomarin, CSL Behring, Novo Nordisk, Pfizer, Roche, and SOBI; **GC:** has served on advisory committees/speaker for Baxalta, Bayer, CSL Behring, Pfizer, SOBI, Novo Nordisk, UniQure, Roche, and Kedrion, and received research support from Pfizer, SOBI, and CSL Behring.

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